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Drug-Induced Changes in Radiopharmaceutical Biodistributions

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DRUG-INDUCED CHANGES IN RADIOPHARMACEUTICAL BIODISTRIBUTIONS

STATEMENT OF OBJECTIVES

Upon completion of this lesson, the reader should be able to:

1. Understand the context in which drug-pharmaceutical interactions occur;
2. Have a broad perspective on the literature of such interactions, and the rigour of our understanding of them;
3. Recognise the classifications of such interactions;
4. Be familiar with the broad outline of the relevant literature;
5. Have a systematic approach in mind in consulting on such interactions either before or after the event.

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Classification of non-radiopharmaceutical or conventional drug-drug interactions

Classification of drug-radiopharmaceutical interactions

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DRUG-INDUCED CHANGES IN RADIOPHARMACEUTICAL BIODISTRIBUTIONS

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INTRODUCTION

Reactions to drugs are well known although it has recently been proposed that they should be classified differently (1). Equally, it has long been recognized that interactions may occur between medications when two or more are administered concurrently (2 – 6). These interactions may change the kinetics, biodistribution or efficacy of conventional medications. From a historical perspective Avery first classified this phenomenon in a systematic way (2). Since then the number of such interactions known to occur has grown dramatically (3 – 6), becoming so important and complex that most physicians now access information about potential drug interactions using electronic databases. It appears that many of these reactions are mediated predictably through the family of isoenzymes known as cytochrome P-450 with some drugs inhibiting and some inducing a P-450 isoenzyme.

However, not all interactions are adverse as, for example, probenecid increases the absorption of orally administered penicillin (7).

Nuclear Medicine and Radiopharmaceuticals

The basis of *in vivo* nuclear medicine practice has been described as follows (8):

"Once a radiopharmaceutical agent is administered to a patient, the biodistribution process occurs. This process consists of the substance's absorption, distribution, metabolism and excretion. When the normal biodistribution pattern of a substance is known, any irregular pattern may suggest the presence of disease."

When radiopharmaceuticals are used as tracers to investigate, diagnose and treat disease, the dose administered is rarely large enough to cause physiological effects. Nevertheless to be effective as markers of some biochemical or molecular process, radiopharmaceuticals must necessarily be biologically active. It follows that they may also be prone to interference from or interaction with concurrent treatment medication(s). Historically in nuclear medicine it became clear that many drugs, iodine containing and otherwise, altered thyroid uptake and thyroid imaging using any and all of the radiotracers in use at any time. In the 1960s and 1970s sporadic reports began to appear of changes in the distribution of radiopharmaceuticals caused by other non-radioactive medications. Since, as noted above (8), the primary purpose of a radiopharmaceutical "drug" is often to examine a tissue or disease process by imaging the distribution of a tracer, the abnormal biodistribution resulting from such an interaction was often immediately obvious.

A few workers, recognizing that this was a systematic and not sporadic problem, began to collect, catalogue, investigate, and report upon such altered biodistributions (8 – 21). Meanwhile the number of accounts of drug-radiopharmaceutical interactions has continued to grow. Currently, a tabulation of such interactions is accessible from the web (20). Unfortunately in the context of a subject that is constantly evolving these catalogues often ignore or are late to recognize findings such as those that relate to newer radiopharmaceuticals such as F-18 fluorodeoxyglucose now coming into widespread use, and newer treatments such as colony stimulating factor in malignant disease.

Initial observations focused on altered tissue and organ distributions. It has also become clear that drug-radiopharmaceutical interactions may change the distribution of the tracer not only in space – that is from organ to organ in the body – but also in time by altering kinetic rate-constants (10, 11).

Classification of Non-Radiopharmaceutical or Conventional Drug-Drug Interactions

Drug interactions have been classified in a number of ways (2, 10, 11, 14) derived from the classification proposed by Avery (2) and a consensus has emerged in favour of a dynamic classification as follows:

- **Pharmacokinetic interactions** occur when the absorption, distribution, metabolic fate or excretion of one drug alters the behaviour of another drug, including such variables as metabolite production, serum concentration, drug excretion and bioavailablity.
- **Pharmacological interactions** occur when the intended or physiological or biological effects of a drug, in its usual dose, alters the physiological action of a second drug.
- **Toxological interactions** result from a side effect or adverse reaction to a drug. These include drug-induced disease, impacting on the serum concentration, bioavailability or other characteristics of a second drug.
- **Pharmaceutical interactions** occur as a result of the physical preparation or suspension of a drug interacting with the preparation or suspension of a second drug.

Classification of Drug-Radiopharmaceutical Interactions

Laven has indicated that the nuclear pharmacist has a substantial responsibility in evaluating and recognizing drug-radiopharmaceutical interactions (22). As the number of drug-radiopharmaceutical interactions has grown it has become increasingly necessary to find a systematic means of classifying them beyond a simple listing. Also, as Hladik and others have pointed out (12), the first distinction to be made in nuclear medicine practice is between intended and unintended effects of medications. It has become commonplace in clinical nuclear medicine to use pharmacological agents to enhance diagnostic procedures – so-called interventional nuclear medicine (23 – 25). Examples are the use of cimetidine to increase the conspicuity of ectopic gastric mucosa, dipyramidole or adenosine to simulate stress blood flow to the myocardium, the use of angiotensin converting enzyme inhibitors in renal investigations and the use of sincalide and morphine in gall-bladder imaging respectively to provoke gall-bladder contraction or contraction of the spincter of Oddi. Some of these procedures may be quite aggressive such as the precipitation of seizure activity during administration of an agent to map cerebral blood flow (25).

A further complication that needs to be borne in mind is that some drugs may modify the effects of the interventional agents used and thus indirectly influence diagnoses reached using radiopharmaceuticals. Thus for example, captopril renography may be misleading in patients in whom a hypotensive response is induced or in those taking calcium antagonists (26 – 28) and caffeine, theophylline and aminophylline may each block dypridamole or adenosine induced coronary vasodilatation leading to false-negative findings when coronary artery disease is being investigated (29, 30).

A second order classification of drug-radiopharmaceutical interactions can be derived from that described above. It needs to be modified for drug-radiopharmaceutical interactions and enhanced as follows:

a) To recognize the impact of tissue toxicity in particular since such toxicities ac-

count for many radiopharmaceutical localizations.

b) To include indirect interactions.
c) To include identifiable changes on imaging which occur by an as yet unknown mechanism. This leads to a group of interactions inevitably described as unknown.

Thus a classification for drug-radiopharmaceutical interactions might be as follows (10, 12):

- Pharmacologic interactions
- Pharmacokinetic interactions
- Pharmaceutical interactions
- Interactions due to tissue toxicity
- Unknown

However, for the purposes of this analysis we have proposed a qualitative pharmacokinetic model that, for analytical purposes, seems to provide a tool to both understand existing drug-pharmaceutical interactions and to analyze those that are now unknown. In drug-radiopharmaceutical interactions the starting point is usually image or alterations in measured function (such as cardiac ejection fraction) which prompt further analysis and thus a simplified pharmacokinetic analysis seems to provide a logical tool which corresponds to the analogous approach to the clinical problem at the "bedside."

Pharmacokinetics

Pharmacokinetic modeling has proved to be a powerful way in which to analyze the distribution, kinetics and behavior of both conventional pharmaceuticals (31, 32) and radiopharmaceuticals (33, 34). At its most elegant such modeling is quantitative in describing the size of the compartments into which drugs distribute and the rate constants for transfer between compartments. While the data on drug-radiopharmaceutical interactions do not support quantitative pharmacokinetic modeling, for the purposes of this review we have used a classification that derives from a qualitative pharmacokinetic model. In practical terms recognizing from imaging that a radiotracer is confined to an abnormal compartment, such as the blood (as in Figure 1) or the interstitial fluid volume (as in Figure 2), can be the first step. This, along with a careful history from the patient, is key to resolving the nature of the interaction. Needless to say both images (Figures 1 and 2) were made with the original intent of examining the skeleton with Tc-99m phosphates. We shall use this pharmacokinetic model to describe a range of effects. The synopsis of reactions listed below also focuses on organs and tissues, not the drugs themselves, consistent with the pharmacokinetic model.

Figure 1. A Tc-99m phosphate bone scan in a patient who had recently been treated with parenteral iron chelate. The tracer has bound to the chelate and is retained in the vascular space with cardiac, hepatic, splenic and major blood vessel visualization and poor signal-to-noise ratio in respect of the intended bone scan (A = anterior views, B = posterior views).

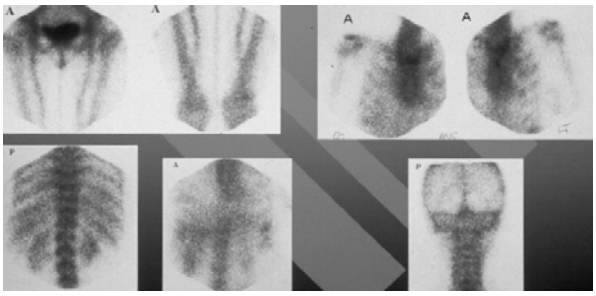
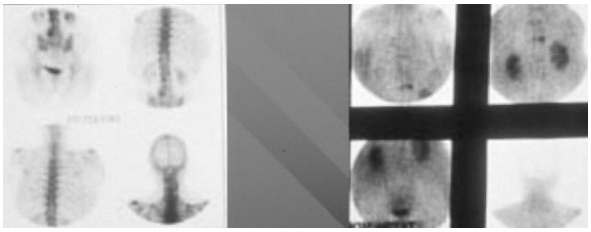


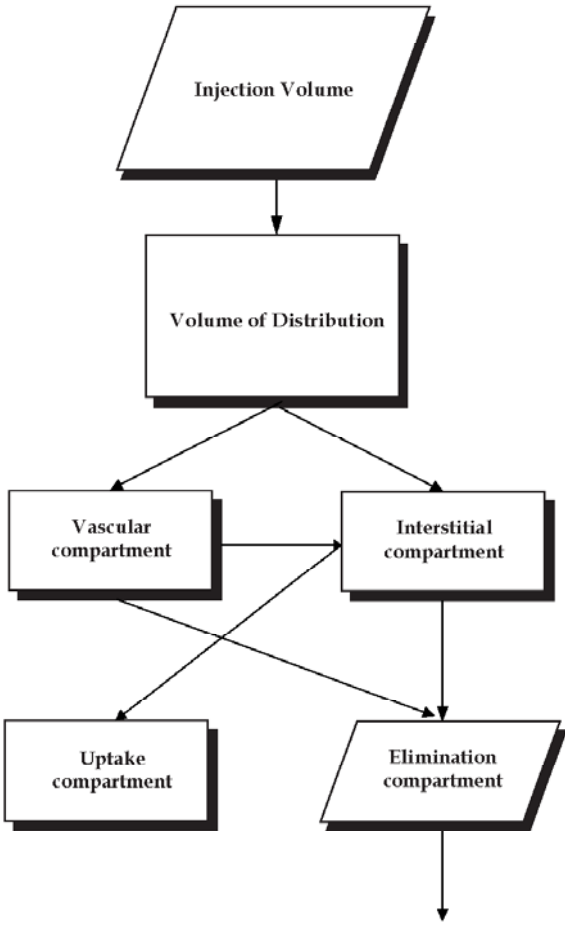
Figure 2. Posterior images from Tc-99m phosphate bone scans in a patient, left, before treatment and, right, while being treated for osteoporosis with etidronate. Skeletal uptake of the tracer in the images on the right is largely imperceptible although at least one metastatic lesion is noted in the upper lumbar spine. The tracer is otherwise uniformly distributed in the interstitial and vascular spaces which are not distinguishable from each other.



The normal pharmacokinetic model is illustrated in Figure 3 and we shall use this as a framework to describe a range of effects in the synopsis of reactions listed below. We will thus focus on compartments, organs and tissues, not on drugs themselves. As previously noted there are web-based resources available to look up particular drug-radiopharmaceutical interactions (19, 20). At the same time the subject of iatrogenic changes in tracer distributions has proved capable of being generalized to include a number of such changes in tracer distributions due, not to drugs, but to radiation, surgery and other physical agents and insults not described here (10, 15).

The lesson to be learned is that anyone examining a nuclear medicine image as an abstraction divorced from the reality of disease, treatment and the patient puts all at risk.

Fig. 3. Normal qualitative pharmacokinetic model.



Evidentiary Basis and Critique

The evidence for drug-radiopharmaceutical interactions is very uneven ranging from prospective studies (often in animals) to single case reports. Given the proper emphasis now being placed on an evidentiary basis for medical practice (35) it is appropriate to consider how much weight should be given to the evidence contained in reports of drug-radiopharmaceutical interactions. Evidence in medical research and practice can be classified as follows:

Table 1. Levels of Evidence [after Meltzer et al. (36)]

Level 1+	Systematic overview or meta-analysis of randomized controlled trials (RCTs)
Level 1-	One RCT with adequate power
Level 2+	Systematic overview or meta-analysis of level 2 RCTs
Level 2-	RCTs that do not meet level 1 criteria
Level 3	Non-randomized clinical trial or cohort study
Level 4	Before-after study, cohort study with non-contemporaneous controls, case controlled study
Level 5	Case-series without controls
Level 6	Case report or case series of <10 patients
The reports analyzed here have been classified using this system but modified to indicate if the data derive from animal (A) or human (H) studies or both (AH).	

To date evidence-based medicine and this tabulation are more usually directed to treatment interventions and outcomes with the emphasis on randomized controlled trials. There is, as yet, no good equivalent in diagnostic medicine. However, the use of the classification in Table 1 serves to suggest the evidentiary basis available to support the case descriptions provided in this synopsis and to illustrate the rigor, or more often the lack thereof, of the analyses reported (35).

In addition it should be noted that not only is the evidence sometimes weak but also the language of the reports is often uncritical. For example, there are publications describing "uptake" of tracers at sites of interstitial injection (see below). Any tracer that distributes into, and has a more than transient residence time in the interstitial space will appear to localize at such sites, but no energy is expended and no "uptake" occurs. A more likely mechanism is that there is a local inflammatory response with a corresponding expansion of the interstitial fluid volume.

Dosage and Bioavailability

It must be noted that there is rarely any critical evaluation of the mechanisms involved or the duration of drug-radiopharmaceutical interactions following cessation of the drug-induced interaction in question. Equally, few studies have examined dose-dependance or other variables. How such interactions impact on the bioavailability of either non-radioactive drug or radio-pharmaceutical is almost never explored. Additionally, while alterations to radiopharmaceutical dosimetry resulting from such interactions have been recognized to occur, most remain unquantified (37).

Site Specificity

While modern pharmaceutical design often provides for site specific agents there is good precedent for such drugs to have unexpected biodistributions and sites of localization (38, 39). Therefore, it is not always practical to analyze drug distributions or drug-radiopharmaceutical interactions on the basis of the anticipated biodistributions of a non-radioactive medication.

A SYNOPSIS OF DRUG-RADIOPHARMACEUTICAL INTERACTIONS

It should be noted that not all unexpected radiotracer distributions are attributable to interactions with concurrent medication. Surgical and other interventions as well as radiation may be evident from radionuclide images (10, 15).

Changes in the Preparation

Some drug-radiopharmaceutical interactions may occur before the radioactive preparation is injected. For example, oxidation of technetium in a syringe of Tc-99m methylene diphosphonate (MDP) may result in visualization of the thyroid gland, gastric mucosa, etc. by virtue of the radiopertechnetate formed (level 6H and *in vitro* data)(40). The same result has been observed from the use of povidone iodine to swab the

septum on a vial of Tc-99m sulfur colloid. Moist antiseptic solution may enter the vial on needle puncture and oxidize the technetium to pertechnetate (level 6H)(41). Aluminum used in syringe manufacture has been found to impact on the stability of radiopharmaceuticals altering their biodistribution (level 6H)(42), while other but unknown syringe extractables may also have a similar effect (level 6H and *in vitro* data)(43).

Further causes of unexpected biodistributions of radiotracer may result from injections inadvertently made intra-arterially, through a catheter or interstitially (all level 6H) (10, 44 – 51). These mishaps usually have typical and predictable appearances on a scan. On at least one occasion, injection into a Swan-Ganz catheter has been reported to result in a false positive lung ventilation-perfusion scan (level 6H)(44). Intra-arterial injection and extravasation has also mimicked disease – regional tumor spread in one report and chronic regional pain syndrome (reflex sympathetic dystrophy) in another – with the potential for diagnostic error (level 6H)(50, 51).

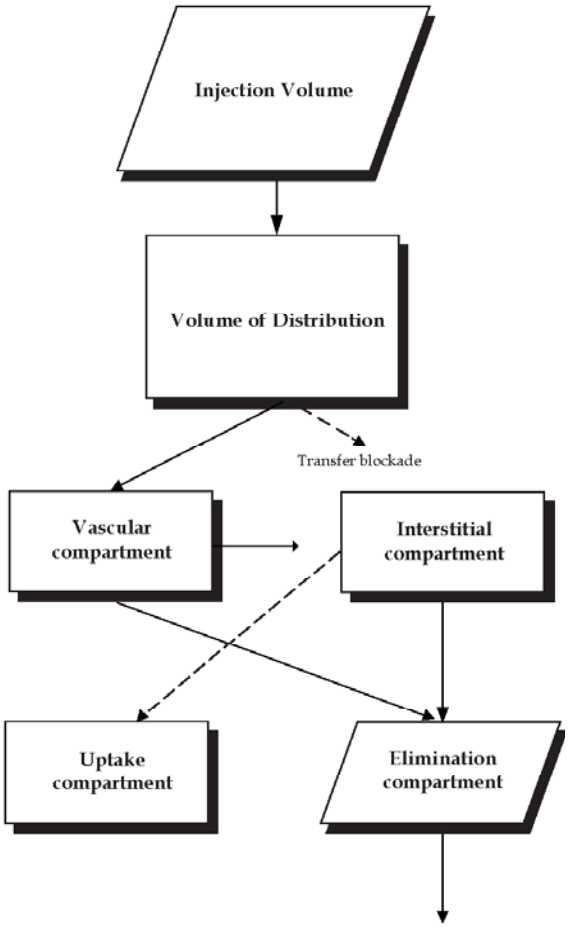
Local Changes Associated with Injection Sites

A number of reports describe that either specific or non-specific interactions between subcutaneous or intramuscular injectates and radiopharmaceuticals may occur to the point of being evident on images. Examples of such reported instances include Tc-99m MDP and radiogallium deposition at an infiltrate of calcium gluconate (level 6H)(52 – 54), Tc-99m phosphates at a site of intramuscular iron dextran (Level 6H)(55, 56) and Tc-99m MDP at sites of heparin administration (level 6H) (57 – 59). It may be argued that some of these interactions are specific in nature. Examples are Tc-99m MDP in binding to calcium gluconate or iron dextran causing trans-chelation and binding of Tc-99m. However, as noted above, a localized inflammatory response may accompany a subcutaneous or intra-muscular injection and will expand the interstitial space at such a site (level 6H) (10, 60 – 62). Therefore, it is to be expected that such lesions may be observed on scan images made using a radiopharmaceutical distributing into that space particularly if it is cleared relatively slowly, with or without an element of specific localization.

Blockade of Transfer

Transfer blockade results from some process that prevents or reduces the amount of the radiopharmaceutical leaving a compartment (usually vascular) following administration (Figure 4).

Figure 4. Qualitative pharmacokinetic model illustrating transfer blockade with retention of the tracer in the vascular compartment.



Bone

When a Tc-99m phosphate is injected in the presence of unusually high serum concentrations of iron (iron dextran) the result is an image in which blood pool predominates with impaired target-to-noise ratios in respect of bone. The supposition is that the technetium is trans-chelated and binds to the dextran, thus becoming trapped in the vascular space (multiple reports, level 6H)(63 – 69) (Figure 1). Penicillamine has been reported to behave in the same way in animal experiments (level 3A) (70). A variation on this theme arises from the therapeutic use of an iron colloid-chondroitin sulfate complex (Blutal, Yuham Co., An Yang, Korea) that appears to bind the technetium by a similar mechanism, but is then phagocytosed into the reticuloendothelial system with a liver image resulting (level 6H)(69).

Disease Identification with Gallium-67

Gallium–67 salts were first explored as potential bone scanning agents and low-specific activity gallium-67 citrate distributes largely into bone. The usefulness of gallium–67 in investigating disease (chiefly malignant and inflammatory processes) only became apparent when high-specific activity gallium was used (71, 72). Although imperfectly understood this mechanism of action appears to depend, in part, on the binding of gallium to transferrin and other serum proteins that bind metals. It appears that if serum concentrations of iron, aluminum or gold are sufficiently high to occupy all of the protein metal-binding sites (and presumably stable gallium plays this role in low-specific activity preparations) then an unusual biodistribution results (level 3A, 5H) (73 – 92) in what has been described as a "gallium bone scan" (90). The abnormally high serum gallium concentrations associated with this phenomenon have been reported to arise either directly from metals (level 5H) (85, 91), or have been attributed to the iron released in cell death by the effective treatment of cancers (levels 4A, 5H) (73, 83, 84, 89, 90), or, in one report, by multiple blood transfusions (level 6H) (86). Moreover, there have been attempts in animals and humans to alter the uptake of gallium in tumors by agents that modulate gallium binding, and such attempts obviously depend upon the timing of the use of agents such as iron or desferoxamine in relation to the gallium-67 injection (74–82, 85, 87, 88).

Initial case reports suggested that gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) used in magnetic resonance imaging (MRI) might also impact on the biodistribution of radiogallium (level 6H) (93), but further evidence suggests this is not the case (levels 3A, 5H) (94–96). Gadolinium salts as such are quite toxic so that the metal as used for MRI contrast is in the form of a non-toxic DTPA chelate so that it would be surprising for the gadolinium to behave as an ion and to competitively bind to serum metallo-binding proteins in competition with gallium.

Blockade of the Target Volume of Distribution

Thyroid: Perhaps the earliest reported, most widely studied, adequately documented and best understood series of drug-radiopharmaceutical interactions are those relating to the thyroid uptake of iodine and radioiodine. In a series of studies dating from the 1940s, it has become apparent that a large number of pharmaceuticals and diagnostic agents impact upon the uptake, organification or retention of iodine by the thyroid gland (97 – 128). Some of these agents are listed in Table 2. They include not only stable iodine itself, but also dessicated thyroid and a number of drugs including the iodine released from the organically bound element in radiographic contrast media. The wealth of evidence and the intuitive nature of the interactions are such that, while most of the data were collected before the era of systematic reviews, most of the evidence is both robust and supported by animal data (equivalent to level 2A, H). It

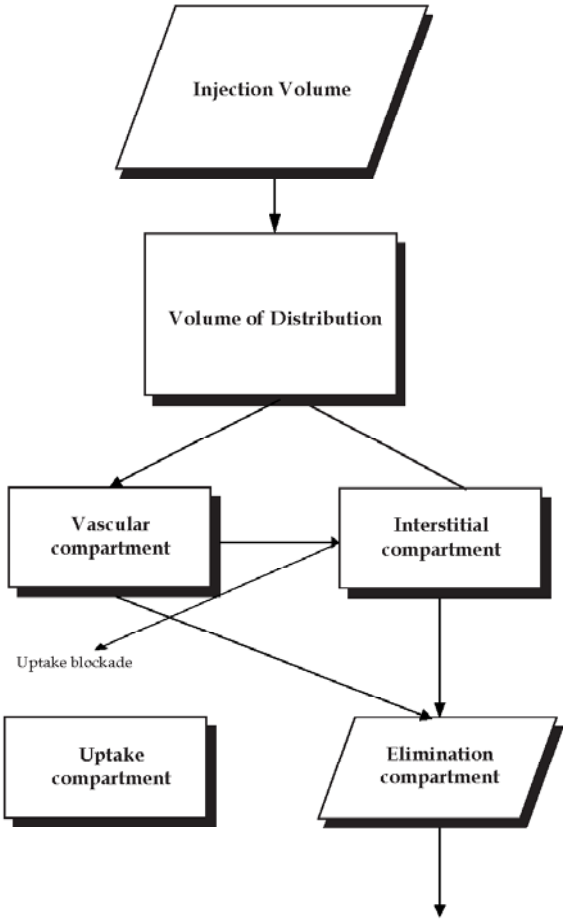
must be noted that exogenous iodine in excess may not only interfere with studies of the thyroid gland using the radioactive iodines but also precipitate thyroid dysfunction.

Table 2. Some Drugs Reported to Negatively Influence Thyroid Uptake of (radio-) Iodine

Anti-thyroide medication, e.g. propylthiouracil	Radiographic contrast media
Amiodarone	Salicylates in large doses
Aminobenzenes	Sodium nitroprusside
Antihistamines	Sulfonamides
Bromides	Thiocyanate
Butazolidin	Topical iodine
Glucocorticoids	Thyroid replacement medication
Iodine-containing medications, e.g. Lugol's solution, potassium iodide, etc.	Vitamin A
Isoniazid	
Nitrates	("herbal remedies" e.g. kelp)
Perchlorate	(Table salt)
Phenylbutazone	(Vitamin-mineral mixtures)

Adrenal medulla: Meta-iodobenylguanidine (MIBG), labeled with I-123 or I-131, has become extensively used in the diagnosis and treatment of disorders of the adrenal medulla and neural-crest-derived tumors, as well as in other applications such as measuring adrenergic cardiac innervation (129, 130). However, the mechanism of uptake is complex and due to two different mechanisms (131 – 133). It is also liable to interference from a wide variety of drugs including some "over-the-counter" medications (levels 3A, H) (134 – 137). Wakabayashi et al. have reported that, in animals, cilazapril and verapamil increase the uptake of radiolabeled MIBG in cardiomyopathy, whereas with progressive disease the reverse is true (level 3A)(138). Equally Meco et al. have found in a human neuroblastoma cell line that cisplatin and doxorubicin block the cell and lead to increased uptake of I-125 MIBG, thereby potentially increasing the radiation dose delivered (in vitro data)(139). Solanki et al. and others have published guides to those drugs that interfere with radioiodinated MIBG uptake and the list tabulated in Table 3 is derived from those publications which should be consulted in full (133, 134, 137, 140).

Figure 5. Qualitative pharmacokinetic model illustrating uptake blockade with retention of the tracer in the vascular compartment.



Adrenal cortex: Adreno-cortical gland function may be imaged and quantified. This is achieved by labeling one of the cholesterol analogues that are precursors of cortisol (141). Again a number of medications either

Table 3. Some Drugs, Including Over-the-Counter Medications, Liable to Influence Adrenal Uptake of Metaiodobenzylguanidine

Antipsychotic medication:	Other antidepressants	Sympathomimetics*
Butyrophenones	Maprotiline	Ephidrine
Droperidol	Trazalone	Phenylephrine
Haloperidol	Bethanidine	Phenylpropanolamine
Pimozine	Bretylium tosylate	Pseudoephidrine
Phenothiazines	Calcium channel blockers	Beta-sympathomimetics
Chlorpromazine	Nifedipine	Albuterol
Fluphenazine	Verapamil	Isoprotenerol
Prochlorperazine	(Cocaine)	Terbutaline
Promethazine	Debrisoquine	Dopamine
Trifluoperazine, etc.	Labetalol	Metaraminol
Thioxanthines	Reserpine	Tricyclic antidepressants
Chlorprothixene		Amitriptyline
Thiothixene		Doxepin
		Imipramine
		Loxapine

*There are theoretical grounds for suspecting that a wider range of this class of drugs should be included such as amphetamine-like drugs.

interfere with or can be used to probe adrenal function, ranging from competitive inhibition by glucocorticoid analogues or the inhibition of 11ß-hydroxylation by metyrapone whereby cholesterol is converted to cortisol (level 3A, 4H)((142 – 146).

Bone: There are a number of case reports indicating that etidronate, the first-generation biphosphonate (or bisphosphonate), used mainly to treat post-menopausal osteoporosis and Paget disease of bone, prevents the normal uptake of Tc-99m labeled bone-seeking agents (levels 4A, 6H)(Fig. 2)(147 - 154). However, one of the second-generation biphosphonates (bisphosphonates) – alendronate - has been studied prospectively in a small trial and does not have this effect (level 3H)(155). Nor does clodrinate, a member of the same drug sub-family although one that is often given intravenously in the treatment of bone metastases as in this particular study (level 4H)(156).

This difference is more realistic than may at first appear to be the case. Second generation bisphosphonates are nitrogen containing and have a different cellular locus of action from etidronate, the first generation drug that is neither nitrogen containing nor as potent as its successors (157). New strategies for modulating bone in the treatment of osteoporosis, either by the potentiation of bisphosphonates (158) or otherwise (159) may modify this conclusion. However, between the mid-1990s and 2004 the second generation of bisphosphonates has been introduced and has become widely used, often replacing etidronate (157). The lack of any case reports (with one exception) to compare with the earlier ones implicating etidronate tends to support the work of Carrasquillo et al. (155) and Koizumi et al. (160) and suggests that their findings are true in respect of all members of the class of second-generation bisphosphonates. The exception is in respect of a single patient reported by Koyano et al. in whom there is uncertainty about the implication of the altered uptake because of co-existing hypercalcemia (level 6H) (161).

Consistent with this, Buja et al. (162) have found in animals that etidronate (EHDP) also interferes with experimental myocardial uptake of Tc-99m phosphates (level 3A).

Hyperphosphatemia has been reported as a result of administering Phospho-Soda for bowel cleansing (163). Saha et al. have attributed the failure of a Tc-99m phosphonate agent to distribute into bone in one patient to daily doses of Phospho-Soda blocking sites of potential bone uptake of the tracer (level 6H) (159).

Brain: Elfving et al. have found, in animal experiments, that all but one [zoletile] of four anesthetic agents they tested modify the cerebral uptake of labeled neuro-receptors (level 3A) (165).

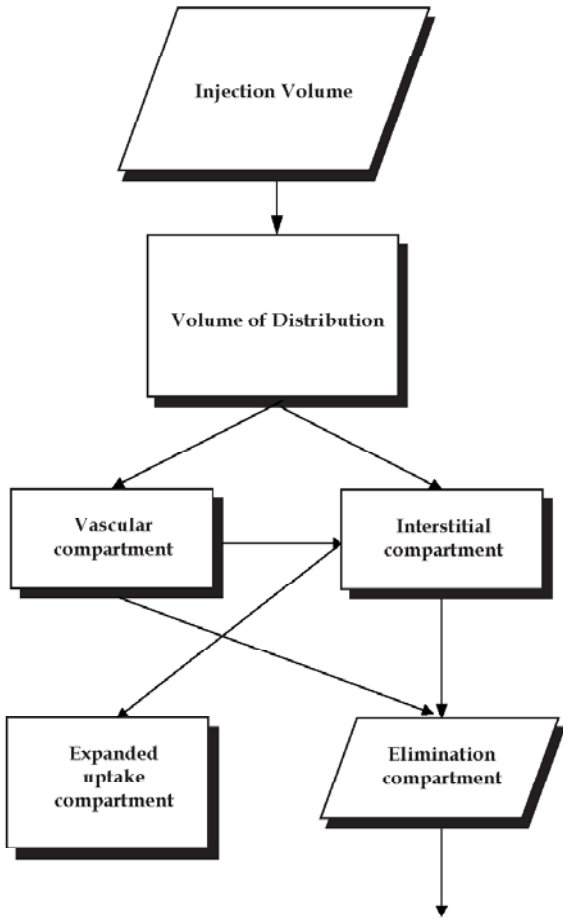
Spleen: Octreotide treatment diminishes splenic uptake by somatostain receptors in a dose related manner (166).

Modification of the Target Volume of Distribution – Expanded Volume

Drugs have been found to modify the target volume of distribution and they may do so either by expanding or decreasing the target volume (Figure 6).

Bone: Tc-99m MDP is typically used to image remodeling bone. Drugs such as isoretinoin that cause bony proliferation have been found to result in images reflecting that proliferation (Level 6H) (167). In case reports, methotrexate became associated with an osteopathy characterized by microfracturing and even gross spinal fracturing all evident not only on imaging with Tc-99m phosphates but also on plain radiographs (level 5H) (168, 169). More recent evidence suggests that these changes are likely the result of marrow infiltration by the malignant disease being treated with methotrexate. The drug itself may either be only partly responsible or not responsible at all. Klingensmith et al. have also found that growth hormone (GH) therapy in GH-deficient children appears to increase the uptake of Tc-99m MDP in bony metaphyses, shafts, and in muscle to a similar extent, and this increase appears to occur in most patients early after initiation of therapy (level 5H) (170).

Figure 6. Qualitative pharmacokinetic model illustrating a modification of the target volume of distribution – its expansion is illustrated.



Osteogenesis imperfecta may be effectively treated with the bisphosphonates (171). In children with growing bones so treated it has been observed that horizontal metaphyseal lines or bands result, on appropriate radiographs, corresponding to episodes of therapy (172 – 4). There is anecdotal evidence that these bands are associated with locally increased uptake pf Tc-99m MDP.

The adequate treatment of bone lesions, chiefly metastases but also osteomalacia,

may result in an initial and paradoxical increase in radionuclide uptake. This has been called the "flare" phenomenon (level 5H) (175 – 188). The temporal evolution of this finding has been incompletely studied but eventually it results in the expected decrease of activity if treatment is effective. Indeed Coleman et al have found that a "flare" is indicative of the efficacy of treatment (182).

Hypervitaminosis D has been found to be a possible cause of a generalized increase in uptake of Tc-99m phosphate in bone (the so-called super-scan) in three patients (level 6H) (189). Also chemoperfusion of a limb has been reported to cause increased activity in bones of the treated extremity by a mechanism that is obscure (level 6H) (190).

Fluorine intoxication resulting from drinking excessive amounts of mineral water has been found to result in increased uptake of Tc-99m MDP in the sternum and bony metaphyses on bone imaging (191).

Glucocorticoids, given in sufficient doses over a long enough period of time, may cause secondary osteoporosis with loss of bone density and increased fracture risk. Severe osteoporosis itself has been associated with a diffuse decrease in Tc-99m MDP uptake in the skeleton presumably reflecting the reduced bone mass (level 6H)(192). However, a further complication of glucocorticoid and/or chemotherapy may result with focal changes in uptake in the femoral head associated with avascular necrosis (level 4H) (193 – 197). Paradoxically there are animal data to suggest that the sensitivity of bone scanning is compromised by glucocorticoid treatment (level 4A) (198).

Bone marrow: Bone marrow hyperemia may be seen on images (such as with Tc-99m chelates used for renal imaging) reflecting either tumor involvement of the marrow space, or marrow regeneration (partly undocumented, 6H) (199). However, with the recognition that "bone" metastases are more often the result of tumor spread into marrow then bone marrow has become of greater interest (200). Notably, F-18 FDG has been found to localize in normal bone marrow induced by colony stimulating factor (CSF) as well as in CSF induced extra-medullary hematopoiesis (level 6H) (201 – 205). Characteristic findings have also been noted in this context on bone imaging (level 6H) (199).

Thymus: The thymus is an organ that perplexed early radiologists because it represented, on chest radiographs of children, an organ they were not used to seeing in adults. It has caused almost as much perplexity in nuclear medicine and several of the reports documented here record diagnostic errors rather than insights. In children before puberty the thymus demonstrates uptake of Ga-67 citrate to a variable extent. Such uptake, as well as that of F-18 FDG, is enhanced not only by chemotherapy of malignant disease but also by treatment of infections (level 5H) (206 – 214). This phenomenon has been described as thymic rebound or regeneration and its specific localization may be made more effective by use of single-photon tomography (203). Given the importance now attributed to the thymus in immunological responsiveness it is not surprising that its metabolic status varies with disease and its treatment. Thus, anterior mediastinal uptake of Ga-67 or F-18 FDG in children should be evaluated with great caution.

Breast: That radionuclides such as the Tc-99m phosphates and Ga-67 citrate localize inconsistently in breast tissue is well recognized (215 – 216). It has been assumed that the degree of breast uptake may relate to timing in the menstrual cycle as well as lactation or breast glandular involution. Breast enlargement (gynecomastia) itself is often drug-related (217). Drugs that typically may induce gynecomastia are estrogen analogues (for example when used to treat prostate cancer) (217). Gynecomastia is particularly associated with enhanced radio-pharmaceutical

uptake and the result is clearly evident on appropriate images (level 6H) (218 – 223).

Modification of the Target Volume of Distribution – Decreased Volume

Bone: Paget disease of bone has long been recognized as a cause of increased uptake of Tc-99m phosphates in affected bone. Successful treatment with mithramycin, first and second generation bisphosphonates (157) or calcitonin may reduce this degree of abnormality (level 5H) (224 – 233). The same is true of the uptake of Ga-67 by Pagetic bone, and Waxman et al. have suggested that this tracer may be a better indicator of therapeutic effectiveness than Tc-99m MDP level 6H) (231, 232). Of interest, none of these reports relating to etidronate indicate the reduced bone uptake otherwise noted and described above (148 – 152).

Crawford and Gumerman have reported that injection of iodine-containing radiographic contrast medium after Tc-99m phosphate is administered intravenously, but before the bone images are made, results in a generalized decrease in uptake of tracer (level 6H) (226). As noted above, there are animal data to suggest that the sensitivity of radionuclide bone imaging is compromised by glucocorticoid treatment (level 4A) (233).

Bone Marrow: Ishibashi et al. report a patient with myelomatosis and increased marrow uptake of thallium–201 thallous chloride. After appropriate chemotherapy the marrow cellular findings improved along with a fall in radiotracer uptake, but of note there was no change in the MRI signal from bone marrow (level 6H) (234).

Liver: Kaplan et al. have reported that about half of 15 patients studied had patchy reductions in uptake of radiocolloid by the liver, altered liver function tests or both after chemotherapy (level 5H)(235). There were equally inconsistent findings in respect of radiocolloid liver imaging in a group of patients with psoriasis treated with long-term methotrexate (level 5H)(236).

Datz lists a number of drugs (phenothiazines, isoniazid, adriamycin, phenobarbitone, testosterone, estrogens, oxacillin, tetracycline, warfarin and toxic doses of vitamin A) as causes of inhomogenous uptake of radiocolloid on liver-spleen scans (level uncertain)(237).

Nicotinamide in large doses is hepatotoxic (238) and has been reported to prevent hepatic extraction and transport of Tc-99m imminodiacetic acid analogues (level 6H) (239), a finding contradicted by Shafer et al. (in vitro data and level 4A)(240). What may be more certain is that hypervitaminosis-A causes discordant liver uptake of radiocolloid and Tc-99m imminodiacetic acid analogues with radiocolloid extraction being preserved (level 6H)(241). But Park et al. question if the same finding they observed when examining hepatocyte function with Ga-67 citrate might be due to the tracers employed rather than the disease in question (level 6H)(242). Hepatic toxicity from erythromycin has also been reported as a rare cause of a false positive scan using a Tc-99m imminodiacetic acid analogue (level 6H)(243).

Sentinel lymph node detection: Vigario et al. have compared, in a prospective study, two groups of patients having lymphoscintigraphy to detect sentinel nodes. One group had had prior chemotherapy; the second was a control group. Using nodal dissection and histology as the reference standard, sensitivity was impaired in the chemotherapy group: seven and one false negative result respectively being encountered ($p = 0.01$)(level 2H) (244).

Tumor imaging: Dextrose administration, like insulin injections within two hours of the radiotracer administration, results in increased uptake of F-18 FDG uptake in muscle but decreased tumor uptake resulting in a decreased standardized uptake value (SUV) (245 – 247).

Creation of an Unexpected Volume of Distribution – Toxicity

This is probably the commonest way in which a medication will manifest itself on a nuclear medicine examination. The unexpected site of distribution usually correlates with either some physiological change or with drug toxicity but it is not necessary for clinical symptoms or other evidence of such toxicity to be apparent before the scan findings are detected. By the same token, radiopharmaceuticals are often more sensitive than radiography. For example, a drug such as bleomycin causes pulmonary interstitial disease ultimately detectable on a chest radiograph. However, in appropriate patients diffuse gallium-67 uptake in the lung may indicate bleomycin pulmonary toxicity despite a "normal" radiograph (level 3H)(10, 248). Of radiopharmaceuticals involved, non-specific disease markers such as gallium-67 are among those most often implicated in the recognition of drug toxicity – emphasizing the role of gallium-67 as a non-specific disease finder.

Colon - pseudomembranous colitis: This inflammatory condition of the large bowel arises from prolonged administration of certain antibiotics. The colon becomes edematous to a degree that may be recognized radiographically. Localization of Tc-99m MDP probably occurs non-specifically because of the expanded interstitial space (level 6H) (249) but the disease may also be recognized on images made with radiopharmaceuticals such as Ga-67 citrate and radiolabeled granulocytes that probe more specific aspects of this disorder that is associated pathologically with inflammatory infiltrates (level 6H) (250 – 253).

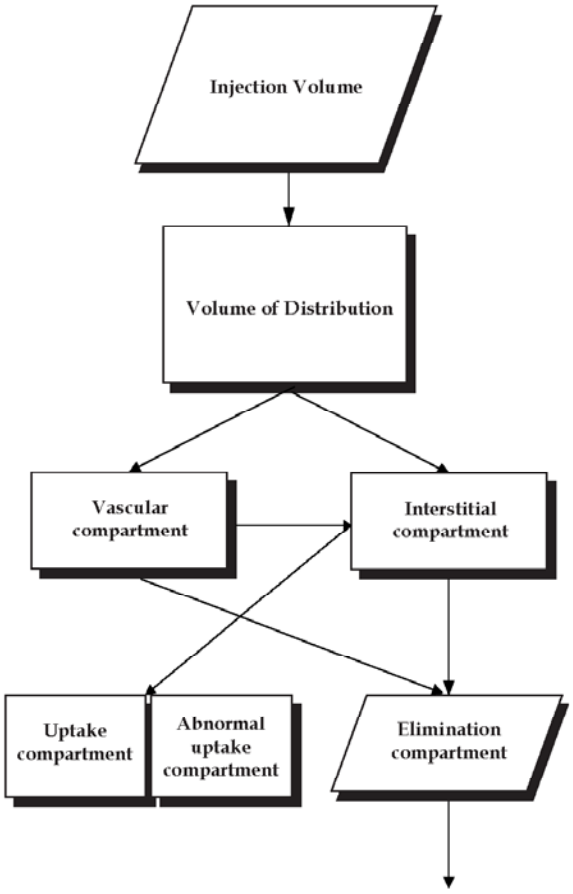
Lung: A number of drugs used chronically cause pulmonary toxicity Some of the agents involved, together with their mechanism of action, so far as is it is understood, are listed in Table 4 (254 – 256). The majority of these have been associated with gallium-67 localization (level 4A,H)(238, 257 – 270). However, such disease has also been detected using labeled granulocytes (level 6H)(271, 272) and F-18 FDG (level 6H) (273). In a prospective study, however, technetium-99m DTPA aerosol scintigraphy has been found to be potentially more sensitive to such changes (level 3H)(274).

Table 4. Drugs Causing Pulmonary Interstitial Disease with an Indication of the Mechanism Involved [after Rossi et al.] (255)

Mechanism of Injury	Drugs Implicated
Diffuse alveolar damage	Bleomycin, busulphan, carmustine, cyclophosphamide, gold salts, mitomycin, and melphalan.
Nonspecific interstitial pneumonia	Amiodarone, carmustine, chlorambucil and methotrexate.
Bronchiolitis obliterans organizing pneumonia	Amiodarone, bleomycin, cyclophosphamide, gold salts, methotrexate, nitrofurantoin, penicillamine and sulfasalazine.
Eosinophilic pneumonia	Nitrofurantoin, nonsteroidal anti-inflammatory drugs, para-aminosalicylic acid, penicillamine and sulfasalazine.
Pulmonary hemorrhage	Anticoagulants, amphotericin B, cyclophosphamide, cytarabine (ara – C) and penicillamine.

Acute lung toxicity resulting from volatile anesthetic gasses has been studied by Hung et al. using Tc-99m hexamethylpropylene amine oxime (HMPAO) and Tc-99m labeled diethylene triamine pentaacetic acid (DTPA). These investigators concluded that halothane and isoflurane caused detectable transient pulmonary vascular endothelium damage as detected using Tc-99m HMPAO and isoflurane caused increased alveolar epithelial permeability as detected using Tc-99m DTPA (level 4H)(275, 276). These observations are of uncertain relevance to clinical practice.

Figure 7. Qualitative pharmacokinetic model illustrating uptake in an expanded volume of distribution (often to be equated with tissue toxicity).



An unusual form of pulmonary toxicity has been reported following contrast lymphangiography – a technique still of some limited usefulness (277). That pulmonary oil embolization results is known to occur (278) and the localization of Ga-67-citrate in the lungs of such patients is consistent with a localized inflammatory response (level 5H) (279).

Heart: The most notable example of drug-related cardiac toxicity is that resulting from adriamycin and its analogues (280, 281). Like ischemic disease of cardiac muscle this results in abnormal myocardial uptake of Tc-99m phosphates (cumulative level 5H)(282-291). Such drug-related cardiac toxicity also results in disturbances of cardiac function recognizable on radionuclide angiocardiography (level 3A,H)(276, 282 - 301).

Muscle: Cardiac toxicity can be considered to be a special case of skeletal muscle toxicity and a number of drugs cause such toxicity and may be recognized on images made with Tc-99m phosphates. Examples of the drugs involved are alpha-interferon, isoretinoin, the statins, epsilon amino caproic acid and ethyl alcohol. The pathological changes induced by the offending drugs are variously reported as a myopathy, polymyositis or rhabdomyolysis but these have in common, as in other contexts, uptake of Tc-99m phosphates (level 6H)(302 - 308) in the abnormal muscle. Again in keeping with findings in respect of the myocardium, the myopathy associated with the statins is not detectable from images made with Tc-99m methoxy isobutyl isonitrile (MIBI) (level 5H)(309).

Kidney: That a number of drugs are nephrotoxic is well known (310). A myriad of reports testify to the fact that Ga-67 citrate localizes to an increased extent in kidneys so affected (level 4A,H)(311 – 322). It is important to realize that the reverse is not true in that this phenomenon is seen in normal kidneys and may not be observed in the presence of disease (317, 323).

Klintmalm et al. have found that cyclosporine renal toxicity in transplant recipients is associated with decreased renal function but relatively preserved perfusion (level 4H)(324). In another study radiolabeled platelets localized uniformly in kidneys with cyclosporine toxicity but with a degree of specificity that provided no diagnostic power (level 4H)(325). In detailed prospective studies, Britto et al. and Shihab-eldeen et al. have demonstrated multi-organ (including renal) toxicity from vincristine and cyclosporine but the changes are of uncertain relevance to clinical practice (level 4A)(326, 327).

Liver: Flynn has reported a single child in whom methotrexate hepatotoxicity resulted in localization of Tc-99m MDP in the liver (level 6H)(328).

Stomach: The impact of vitamin D intoxication on the skeleton has been noted above (189) but there is also a report of massive gastric uptake of Tc-99m MDP as a result of excessive uptake of vitamin D in health food supplements and milk. The finding resolved with cessation of the administration (329)

Multiple organs: Havens et al. have reported a patient with an overdose of chloroquine in whom Ga-67 uptake was noted at the several sites of the known organ toxicity of this drug (level 6H)(330).

Creation of an Unexpected Volume of Distribution – Non-Toxic

Tumor or disease imaging – splenic visualization: As noted previously, F-18 FDG imaging will reflect bone marrow regeneration and metabolic activity resulting from administration of CSF (201 – 205). Incidental to imaging with the same tracer, there has been observed extra-medullary hematopoiesis in the spleen, and potentially this may occur at other such sites (level 6H)(331, 332).

Tumor or disease imaging – lung visualization: Bacillus Calmette-Geurin (BCG) has been administered to provoke an immunological response to cancer. A pneumonitis has been observed as a result (333, 334), as well as more recently in a patient treated with BCG for superficial bladder cancer (335). There are data to indicate that lung uptake of Ga-67 citrate will reflect pneumonitis as might be anticipated (level 4H,A)(334, 336, 337).

Tumor or disease imaging – lymph node visualization: Phenytoin is known to induce lymph node hyperplasia in some patients – a phenomenon that has been found to be reflected in detectable increases in Ga-67 citrate uptake in the hilar lymph nodes of such patients (level 3H)(338).

Paradoxical changes in pulmonary perfusion: Heparin is typically administered to reduce venous clotting and prevent pulmonary thrombo-embolism. In a small subset (about 1%) of patients, a thrombocytopenia results with thrombotic complications (the so-called "white clot" syndrome) leading to embolization and a worsening of pulmonary perfusion as imaged by Tc-99m macroaggregates (cumulative level 3H)(339 – 342).

Bone imaging – metastatic calcification: Hypercalcemia is recognized to result in soft-tissue "metastatic" calcification – typically occurring in the kidneys, lungs and stomach, but less often in other organs and tissues. Such sites are identifiable on bone scans. Listed causes include some medications and disease states such as hypervitaminosis D, phosphates and glucocorticoids as well as milk-alkali syndrome which may be contributed to by antacids (level of evidence uncertain)(343).

Bone imaging – liver visualization: Poulton has observed intravenously injected iohexol to cause Tc-99m MDP to localize in the liver and spleen (level 6H)(344). However, a much more widely investigated example of this is due to increased serum aluminum concentrations including those that result from antacid medications (level 4A,H) (345 – 350).

As previously noted the use of an iron colloid-chondroitin sulfate complex (Blutal, Yuham Co., An Yang, Korea) appears to bind Tc-99m MDP by transchelation and the resulting particulate is phagocytosed into the reticuloendothelial system (level 6H)(69).

Bone imaging – renal visualization: Lutrin et al. observed intense renal parenchymal uptake of radioactivity in 17 of 265 bone scans done in children receiving chemotherapy for various malignant diseases. In a retrospective analysis, it was found that uptake occurred when imaging was performed

within one week of cancer chemotherapy with cyclophosphamide ($p < 0.05$), vincristine ($p < 0.01$), and doxorubicin ($p < 0.02$). None of the 265 scans showed intense renal uptake unless the patient received chemotherapeutic drugs in the preceding week. This finding did not seem to result from altered renal function, and the exact cause has not been defined (level 4H)(351). This finding was echoed in a report from Trackler in respect of amphotericin B therapy (level 6H) (352, 353). McAfee et al. found that increased renal uptake of 99m-Tc MDP was observed irregularly in rats after methotrexate, vincristine or gentamicin, administered separately. Cisplatin regularly induced a dose-related increase in renal uptake of Tc-99m MDP that correlated with the degree of tubular damage histologically. The augmented renal uptake of Tc-99m MDP was not consistently accompanied by a decreased clearance of simultaneously injected I-131 iodohippurate, particularly at lower drug dose levels. These investigators concluded that in this model drug-induced renal retention of MDP by a factor of two or more above normal appears to be a useful indicator of tubular damage when other parameters of renal function are sometimes normal (level 4A)(354). Chen et al. report that Tc-99m MDP-gentamycin interactions can be averted in respect of this nephrotoxic agent by monitoring plasma levels of gentamycin (level 3H) (355).

McRae et al. report that sodium gluconate causes bone-seeking tracers to transform into Tc-99m gluconate and localize in the kidney. This reaction is accelerated by injected calcium and iron (in the ferrous state) lending support to the observations above concerning the interaction of iron and bone scanning agents (level 5H)(356).

Bone imaging – the sickle sign: A side-effect of intensive cytotoxic treatment on bone scanning that Creutzig and Dach choose to call the "sickle sign" amounts to a diffuse activity over the calvarium seen only in patients receiving this therapy. It is distinguishable from metastases by a vertex view in which the activity is uniform not patchy. Although not advanced by the authors, a possible explanation is that of marrow activation or extension in response to the treatment (level 6H)(357).

Bone imaging – abdominal activity: McDevitt et al. report a patient who had a Tc-99m MDP bone scan while on continuous ambulatory dialysis. Diffuse abdominal activity was noted. The investigators hypothesize that the Tc-99m MDP diffused across the peritoneal membrane. They were able to show that diffusion will occur across a semi-permeable membrane (in vitro data, level 6H) (358).

Bone imaging – blood pool visualization: The amount of stannous ion in a bone scan preparation may be sufficient to reduce the technetium, either in the preparation or administered separately as sodium Tc-99m pertechnetate, resulting in red blood cell radiolabelling (see below) and yielding images with varying degrees of blood pool visualization (level 3H)(359, 360).

Renal imaging – gall-bladder visualization: Hinkle et al. carried out a chart review looking for patterns of altered biodistribution of Tc-99m glucoheptonate associated with other factors. The data did suggest the possibility that penicillamine, penicillin G potassium, penicillin V potassium, acetaminophen, and trimethoprim-sulfamethoxazole might cause increased hepatobiliary clearance of the radiopharmaceutical. Subsequent animal tests showed that i.v. penicillamine caused substantial distribution of radioactivity into the gallbladder and small bowel (level 4AH) (361).

Planar brain imaging – visualization of blood-brain barrier defects: Brain edema and the blood brain barrier relate to planar imaging which is no longer greatly used. However, there are data respecting “drug”

effects that may be relevant to other methods of examining the brain. Cerebral edema may be due to either intracellular or extracellular fluid accumulation (362). The latter is typically seen in tumors. However, vascular permeability in the brain may be increased in the short term by contrast agents used in cerebral angiography and demonstrated by radionuclide brain imaging (level 6H)(363). At 24 hours post-administration the alteration in vascular permeability may no longer be evident (level 6H)(364). Methotrexate or other cancer chemotherapy, administered systemically or intrathecally, also causes brain toxicity with abnormal findings in patients in whom the blood-brain barrier is challenged with radiopharmaceuticals (level 6H)(365 – 367). A further effect of medication in this context is that of glucocorticoids which reduce blood-brain barrier permeability in disease and thus decrease the conspicuity of brain tumors and metastases upon diagnostic images, which also includes their imaging with Ga-67 citrate (level 4H and 6H and correlative CT)(368 – 373).

Xenon ventilation imaging – visualization of liver and bone marrow: While chemically inert xenon is very fat soluble (374) and dissolves in blood, it may then localize in fatty deposits such as focal and diffuse liver steatosis (375) and in fatty infiltration of bone marrow. Xenon-133 uptake in liver steatosis resulting from hepatotoxic medication has either been reported, or there are theoretical grounds to believe it may occur, in patients on clofibrate medication or receiving total parenteral nutrition (level 6H) (376 – 381). In the same way bone marrow uptake of xenon-133 has been observed (382). In one patient reported by Katz et al. the only potential explanation was the fatty marrow replacement known to result from long-term glucocorticoid therapy (level 6H) (383).

Pertechnetate imaging of thyroid, ectopic gastric mucosa, etc. – visualization of blood pool: Sulfonamides, aluminum containing antacids (or any cause of hyperaluminemia) and, as previously noted, preparations containing an excess of stannous ions have the potential to result in labeling of red blood cells (359, 360). Tin (SnII) does this by reducing the Tc-99m sodium pertechnetate (385 – 390) but the mechanisms of action of aluminum (347) and sulphonamides (390) are unknown (level 3H).

Labeling of red blood cells (in vitro and in vivo) – poor labeling efficiency: A great variety of drugs (see Table 5) impair the efficiency of red cell radiolabeling (in vitro data, levels 4H,A)(390 – 410). Mechanisms for some have been proposed (14) but little is known, not only of the mechanisms involved but also dose effects or temporal factors (400). Indeed data are often conflicting. However, in a report unusual in that it describes negative findings, Nascimento Cardosa et al. report that they found no effect of propanalol, cyclosporine, adriamycin, and nifedipine on in vitro labeling (410) and in general in vitro methods tend to minimize these drug-induced constraints.

Table 5. Drugs that Influence the Efficiency of Red Cell Radiolabeling

Adriamycin	Iodinated contrast agents
(Blood transfusions)	Prazosin
Digoxin	Sulphonamides
Heparin	Some anti-neoplasic agents

Labeling of white blood cells – poor labeling efficiency: MacGregor et al. have observed inhibition of granulocyte adherence and false negative results in patients treated with lidocaine (in vitro data, 4H)(411). Thakur et al. have found reduced chemotaxis in labeled white cells exposed to lidocaine and procainamide (in vitro data)(412). There are theoretical grounds (10) and some limited clinical data to suggest that antibiotics and glucocorticoids may also interfere with radiolabeling of white blood cells but the limita-

tion is clearly not absolute (413 – 414). This subject has been reviewed by Sampson (415).

Labeling of platelets – poor labeling efficiency: Heparin therapy in adequate doses has been reported to impair the use of labeled platelets to identify propagating thrombi – a result consistent with the known actions of this drug (level 4AH)(416 – 418).

Liver imaging – lung trapping of radio-colloid: Aluminum ions from medication may be absorbed into the blood in amounts sufficient to cause aggregation of radiocolloid which then traps in pulmonary capillaries (level 5H, as noted in one study of a patient who served as his or her own control) (419 – 423).

Drug Interference with Radiopharmaceutical Studies of Organ Kinetics

There are many drugs used to modify organ kinetics. The numerous therapeutic approaches to the modification of cardiac function represent an example. This is not the place to provide a primer describing such drugs. Instead the focus will be on the potential for drugs to cause misleading findings.

Renal: Clorius et al**.** in a study of renal grafts found that furosemide significantly influenced renography – an observation that is almost intuitive (level 4H)(424). Yee et al. found that ammonium chloride, mannitol and sodium bicarbonate changed the distribution of Tc-99m DMSA between liver and kidney in favor of the liver so that renal quantitation might be modified by the patient's hydration state (level 3A)(425). Fritzberg et al. and Gomes et al., in human and animal experiments respectively, provide further evidence of the need to control for medication and other physiological variables in renal studies (426, 427).

Ventilation: Sedation has, for example, been shown to alter the distribution and dynamics of ventilation in man as studied with xenon-127, chiefly in reducing functional residual capacity (level 5H)(428).

Biliary: Biliary studies are typically carried out with pharmacological intervention, as in the use of phenobarbitone in evaluations of neonatal jaundice (429, 430). Biliary studies are typically done for the diagnosis of cholecystitis with cystic duct obstruction (431) and, if there is gall-bladder filling, biliary contraction may be studied after administration of the active fragment of cholecystokinin (432). However, of note false positive biliary studies with absent gall-bladder filling have been reported as due to alcoholism, total parenteral nutrition, and erythromycin hepato-toxicity and possibly nicotinic acid toxicity (level 6H)(239, 240, 433 – 435). Narcotics are known to cause the appearance of biliary obstruction by inducing contraction of the spincter of Oddi (436 – 440), but this is reversible with naloxone (441). Householder et al. found scintigraphic evidence of the chemical cholecystitis known to occur with hepatic infusion chemotherapy in all ten of the patients they investigated (level 5H)(442).

Cerebral blood flow: The importance of controlling for drug therapy in receptor and blood flow studies of the brain is illustrated by the literature on positron emission tomographic research studies of the brain, but such factors apply to studies with single-photon emission computed tomography as well (level 3AH)(443 – 444).

Gastric emptying: Radionuclide methods have become the preferred way to measure gastric emptying (445 – 447). In using the techniques available, however, it is necessary to recognize the large number of drugs (see Table 6) (448) that alter gastric motility by increasing or decreasing the rate of emptying (449 – 461). The mechanisms are diverse, often poorly understood and have been examined by Hladik et al. (10). Virtually all of the data derives from clinical studies (level 5H) and the subject has been reviewed by Chaudhuri and Fink (461).

Table 6. Some Drugs Which are Known to Prolong Gastric Emptying

Aluminum hydroxide gel	Pentazocine (rat)
Antacids (other)	Metoclopramide
Anticholinergics	Morphine (narcotic analgesics)
Atropine (aerosolized)	Propantheline
Levodopa	Total parenteral nutrition
Nalbuphine (rat)	

Myocardial perfusion: Radionuclide methods are important in examining myocardial perfusion (462, 463) and contractility (464). The drugs modifying both are usually used as treatment interventions and are well understood, both in respect of perfusion imaging (variable, but in general level 2H)(462 – 484) and function (variable, but in general level 2H)(478, 485 – 502). Nevertheless, having an understanding of cardiac hemodynamics and these drug effects are critical to the clinical use of these radionuclide methods.

Gastric mucosa: Several drugs such as cimetidine, pentagastrin, glucagons and secretin are known to modify Tc-99m pertechnetate uptake by gastric mucosa and are used in nuclear medicine to enhance detection of ectopic gastric mucosa. Their effects are unlikely to be serendipitous. (level 3H) (503 – 506).

Gastroesophageal reflux: Reflux may be measured before and after treatment (507). Little or nothing is known of drug effects in this context which are incidental.

EFFECTS WHEN RADIOTRACERS ARE ADMINISTERED OTHER THAN INTRAVENOUSLY

Cerebro-spinal fluid studies: Cerebro-spinal fluid (CSF) dynamics are altered by acetazolamide (Diamox) with the potential to result in misdiagnosis from studies of CSF flow. Acetazolamide inhibits the enzyme carbonic anhydrase and causes vaso-constriction of blood vessels in the choroid plexus tending to reduce the production of cerebro-spinal fluid. Papanicolaou has reported abnormal cisternographic findings attributed to this cause (level 6H with the patient acting as his or her own control)(508).

ALTERNATIVE MEDICINE AND SELF-MEDICATION

Not all the drugs being consumed or the treatments used by people will be conventional physician-prescribed medications or catalogued in the US Pharmacopeia (USP). Awareness of this may clarify some unexpected scan findings. Acupuncture, for example, if used adjacent to bone has been found to excite a local bony reaction on scans made with Tc-99m MDP and I-131 sodium iodide (level 6H)(509, 510). Sites of injection of mistletoe have been observed on In-111 satumomab pendetide imaging (level 6H)(511) while *Ginkgo biloba*, used in herbal medicine, impacts on the labeling of red blood cells (in vitro data)(407).

The impact of recreational drugs on radiotracer biodistributions also threatens to become a topic in its own right. For example, there is an as yet obscure syndrome of increased skeletal mass and bone density with increased uptake of bone seeking agents, probably related in some or all of the patients to infection with hepatitis-C, that has been described in intravenous recreational drug users (level 2H)(512 – 514). Ex-heroin users have been found to have pulmonary vascular disease detectable by scintigraphy (level 5H)(515 – 517). “Crack” cocaine alters pulmonary alveolar permeability (level 3H) (518), as well as causing abnormalities of brain perfusion (level 5H)(519).

Another street drug, “ecstasy”, has been found to modify cerebral receptor imaging in the brain (level 3H)(520). Heroin-induced rhabdomyolysis has been observed to cause chronic regional pain syndrome (formerly known as reflex sympathetic dystrophy) and recognized from bone scintigraphy (level

6H)(521). However, drugs that are more generally sanctioned by society such as the caffeine in coffee (level 5H)(29), tobacco (403) or the smoke from cigarettes (level 4H) (5, 522) and alcohol (307, 433) have also been found to leave signatures on radiopharmaceutical kinetics or biodistributions. Generalizations are to be avoided in that, for example, chronic smoking appears to slow gastric emptying, but a similar finding does not result from the use of nicotine in chewing-gum (level 5H)(524).

Excessive self-medication may also result in changes to radiopharmaceutical distributions. Vitamin D, already noted to influence the biodistribution of Tc-99m phosphates (189), may reach toxic concentrations from the compulsive ingestion of health food supplements and milk. In one patient reported the result was massive uptake of Tc-99m MDP in the stomach (level 6H)(329). In another patient drinking an excess of mineral water resulted over time in fluorine intoxication and fluorosis resulting in intense uptake of Tc-99m MDP in the axial skeleton, bone metaphyses and sternum (level 6H)(191).

To anyone used to working in a clinical setting, the value of careful history-taking has always been apparent and such observations serve to further emphasize that fact.

THE FUTURE

There is evidence that prospective studies of drug-radiopharmaceutical interactions (525 – 528) are being undertaken and even attempts made to model these interactions (513) so that published reports offer useful clinical data and thus become less anecdotal. As designer pharmaceuticals become more specific in their actions then their interactions with radiopharmaceuticals may tend to diminish in number and intensity. The contrary may prove true for the continued development and use of probes in nuclear medicine. Imaging procedures using these agents will become more sensitive to subtle changes in physiological processes will increase the need, in proportion, for radiopharmacists and nuclear medicine physicians to control all of the patient-related variables, not just those due to medication alone.

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QUESTIONS

1. Which of the following does NOT characterize drug interactions:
   a. Interactions require pharmacologically similar agents.
   b. They are dose related.
   c. Many are mediated by a family of isoenzymes known as cytochrome P-450.
   d. They may occur independently of hepatic or renal clearance.

2. On a Tc-99m MDP bone scan there is radiopharmaceutical localization in lymph nodes in the right axilla. Your first reaction should be:
   a. To examine the patient to determine if there is lymph node enlargement.
   b. To examine the patient's chart to determine if there is tumor involvement of the axillary nodes.
   c. To examine the quality control data concerning that particular preparation.
   d. To image the injection site to evaluate the possibility that part of the dose was injected interstitially.

3. An evidentiary basis for medical practice optimally requires:
   a. An agreement by experts.
   b. Syntheses of prospective studies of adequate power.
   c. A randomized control trial.
   d. Legal sanction of drug interventions.

4. Patients being treated for cancer may be given colony stimulating factor (CSF). In their follow-up, a positron emission tomography examination may be done using F-18 fluorodeoxyglucose. If abnormally increased uptake is then seen in the spleen, which of the following do you most suspect:
   a. An immunological response.
   b. Extramedullary hematopoiesis.
   c. Splenic chemotherapeutic toxicity.
   d. Tumor recurrence in the spleen.

5. For a radiopharmaceutical to be found to localize at the site of intramuscular injection of another drug which of the following conditions may be necessary:
   a. Some physiological or chemical interaction of drug and pharmaceutical.
   b. A localized inflammatory response.
   c. A radiopharmaceutical which clears from the tissues in hours rather than in minutes.
   d. All of the above

6. Drug-induced lung toxicity is compatible with all of the following except:
   a. The patient in question is being treated with bleomycin.
   b. The patient in question is being treated with nitrofurantoin.
   c. The chest radiograph is normal.
   d. On a scan with gallium-67 citrate any uptake in the lung is focal.

7. Which of the following statements about intravenous radiological contrast media is untrue:
   a. Their radio-opacity in sufficient concentration is due to their electron density as a result of their iodine content.
   b. The iodine remains 100%bound and thus has no physiological impact on the thyroid gland.
   c. Gadolinium chelates used in magnetic resonance imaging have not been proven to alter the biodistribution of radiopharmaceuticals.
   d. When used clinically they alter capillary permeability distal to the injection site.

8. Diphosphonates (or bisphosphonates) are used both in nuclear medicine diagnosis (labeled with Tc-99m) and the treatment of post-menopausal osteoporosis, cancer,

Paget disease of bone, etc. In appropriate patients the radiopharmaceutical and drug may interact except in which circumstance:

a. The patient has normal bone density.
b. The therapeutic diphosphonate is nitrogen containing.
c. The treatment is weekly rather than daily.
d. Bone turnover is not increased.

9. Receptor-mediated uptake of radiopharmaceuticals is a powerful tool in investigating physiological and pathological processes. It is, however, subject to competitive inhibition by appropriate drugs as in all but which of the following circumstances:

a. Thyroid uptake of iodine.
b. Adrenal uptake of metaiodobenzylguanidine.
c. Brain uptake of I-123 iodoamphetamine.
d. Tumor uptake of labeled octreotide.

10. The thymus gland is involved in the development of immunity and it involutes in adulthood. Thymic uptake of gallium-67 citrate may be seen in all but which of the following circumstances:

a. In normal children.
b. In some thymic tumors (thymomas).
c. In all patients with myasthenia gravis.
d. In some children on completion of a course of chemotherapy.

11. The intravenous injection of street drugs ("mainlining") with contaminated needles may lead to hepatitis-C infection and all but one of the following potential consequences:

a. A syndrome of increased bone density.
b. Pulmonary disease characterized by unusual uptake of gallium-67 citrate.
c. Reduced liver extraction of Tc-99m colloid and IDA analogues.
d. Impaired gall-bladder contractility.

12. Abnormally great localization of Tc-99m MDP in the kidneys has been observed in which of the following circumstance(s):

a. Within 24 hours of injection of radiological contrast media.
b. Cyclophosphamide treatment.
c. After injection of iron-containing compounds.
d. All of the above.

13. Muscle disease (myopathy, polymyositis or rhabdomyolyis) may occur as a result of drug treatment, and may then be identified as abnormal muscle uptake of Tc-99m MDP on a bone scan, in which of the following circumstances:

a. Simvastatin therapy.
b. Alpha –interferon therapy.
c. Epsilon amino caproic acid therapy.
d. All of the above.

14. An image of the blood pool may result when a bone scan is intended after a Tc99m phosphate injection. A possible cause you might examine includes which of the following:

a. An excess of tin (SnII) in the injectate or in a prior injection of Tc-99m pertechnetate leading to labeling of red cells in vivo.
b. Recent administration of iron dextran (FeII), or similar compounds given for therapeutic reasons, resulting in probable trans-chelation of the Tc-99m.
c. Recent administration of sodium phosphate laxative.
d. All of the above.

15. In vitro labeling of red blood cells may be preferred over the in vivo technique

because of which of the following reasons:

a. The potential of drugs to interfere with Tc-99m binding is minimized.
b. The method is independent of the specific activity of the Tc-99m.
c. The patients red cell volume is unimportant.
d. The binding of the tracer is stable.

16. In considering drug-radiopharmaceutical interactions, which of the following statements is true:
    a. Little is known of the bioavailability of radiopharmaceuticals in patients on treatments that alter their biodistributions.
    b. Rarely are there data about the duration of drug-radiopharmaceutical interactions.
    c. Rarely are there data about the dose dependancy of drug-radiopharmaceutical interactions.
    d. All of the above.

17. Uptake of I-123 iodine in the thyroid is reduced by:
    a. Application of tincture of iodine (Lugol's) to the skin.
    b. Thyroid stimulating hormone.
    c. Amiodarone.
    d. All of the above.

18. In considering drug-radiopharmaceutical interactions which of the following statements is true:
    a. The documented dosimetry of the radiopharmaceutical becomes invalid.
    b. The non-radioactive drug involved suffers impaired efficacy.
    c. Such interactions only occur when drugs are administered in toxic doses.
    d. All of the above.

19. New bone formation, detectable on Tc-99m methylene diphosphonate images and radiographs, may be a side effect of which of the following medications:
    a. Vitamin D.
    b. Methotrexate.
    c. Non-steroidal anti-inflammatory medication.
    d. All of the above.

20. Drug toxicity is most often seen as an incidental finding on images made with:
    a. Tc-99m methylene diphosphonate.
    b. F-18 fluorodeoxyglucose.
    c. Ga-67 citrate.
    d. In-111 and Tc-99m labeled granulocytes.

21. Tc-99m phosphates may be imaged as localizing in soft-tissue disease in which of the following situations:
    a. Myocardial infarction.
    b. Adriamycin induced cardiotoxicity.
    c. Alpha – interferon therapy.
    d. All of the above.

22. The biodistribution of gallium-67 citrate is commonly modified by:
    a. An excess of metallic cations such as iron in the blood.
    b. Cancer chemotherapy.
    c. Antibiotic-induced renal toxicity.
    d. All of the above.

23. Localization of I-123 metaiodobenzylguanidine in the adrenal medulla is reduced by:
    a. Labetalol.
    b. Tricyclic antidepressants.
    c. Reserpine.
    d. All of the above.

24. Sites of tissue toxicity detectable by Tc-99m chelates include which of the following:
    a. Pseudomembranous colitis.
    b. Antibiotic induced nephrotoxicity.

c. Drug-induced myopathy.
d. All of the above.

25. Hyperaluminemia, including that resulting from medications containing aluminum, may result in which of the following radiopharmaceuticals having altered biodistributions:
a. Tc-99m phosphates.
b. Tc-99m sulfur colloids.
c. Ga-67 citrate.
d. All of the above.